SYNTHESIS OF 7-ETHYL-1,2-DIHYDROQUINOLIN-2-ONES AS ANGIOTENSIN II RECEPTOR ANTAGONISTS†

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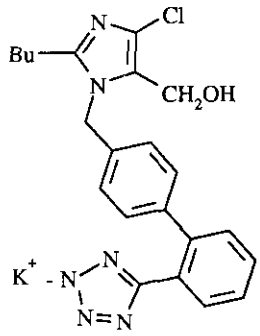
Abstract - A number of biphenyl substituted 1,2-dihydroquinolin-2-ones were synthesized by regiospecific alkylation of the corresponding 1H-derivatives. Again, these precursors were prepared in three steps by acetoacetylation of anilines, regiospecific C-alkylation of the resulting ß-ketoanilides and subsequent condensation to the quinolinones. One of the target compounds, 2-[7-ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]-N,N-dimethylacetamide (**10e**), is a potent angiotensin II receptor antagonist.

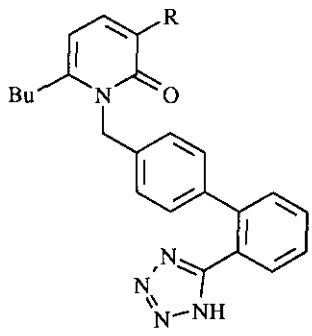
The tetrasubstituted imidazole losartan (**DuP 753**) is the prototype of potent, selective and orally active non-peptide angiotensin II receptor antagonists.[1] This compound is currently in clinical trials as an agent for the treatment of hypertension.[2] The alkyl chain and the biphenyltetrazole attached to the imidazole ring are the key structural features within this class of drugs. The imidazole moiety, however, can be replaced by a number of other heterocycles such as benzimidazoles,[3] imidazopyridines,[4] 1,2,4-triazoles[5] or 4-aminopyridines.[6] As part of a survey to peplace the potential imidazole moiety with other heterocyclic groups, we synthesized 3-substituted pyridones (**1**),[7] which were found to be potent antagonists of angiotensin II. We were also interested in making rigid analogues of **1** by forming a ring between the pyridone nucleus and the butyl chain to provide quinolinones (**2**) with the alkyl chain attached to the 7-position. In this paper we report the syntheses and in vitro properties of selected 3,4,7-trisubstituted 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihy-

† Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.

droquinolin-2-ones as angiotensin II antagonists.



DuP 753



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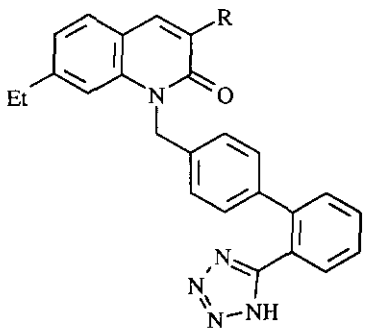

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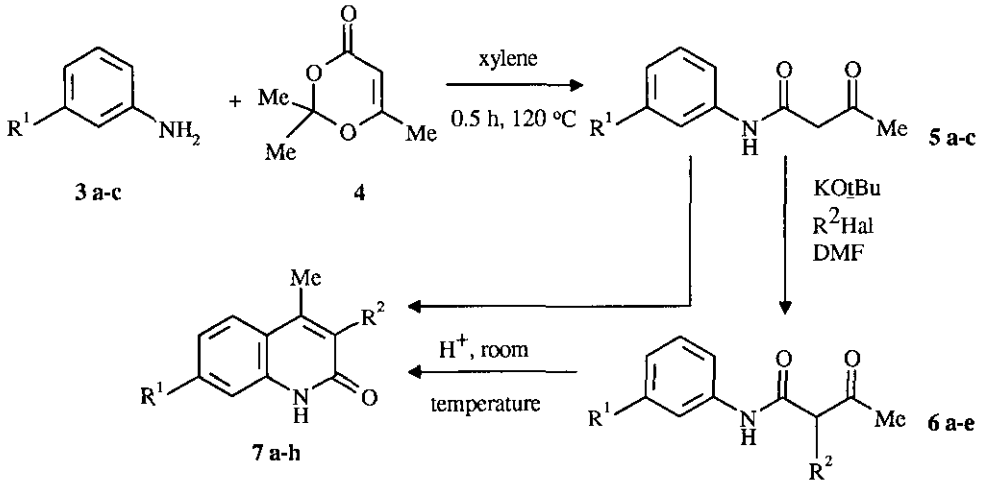
Two methods have been established for the preparation of a wide range of 3,7-disubstituted 1,2-dihydroquinolin-2-ones: Condensation of malonates with anilines leading to 4-hydroxy derivatives[8] and condensation of anilines with ethyl 2-alkylacetoacetates giving rise to 4-methyl derivatives.[9] On account of broad variations in the 3-position we sought for a reliable method for the preparation of this ring system. We utilized the previously reported Knorr cyclization of an acetoacetanilide derivative obtained from o-anisidine and diketene.[10] Instead of diketene the commercially available 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**4**) (dioxinone) was used.[11]

The synthesis of 3,7-disubstituted 1,2-dihydroquinolin-2-one intermediates was carried out according to Scheme I.

Scheme I

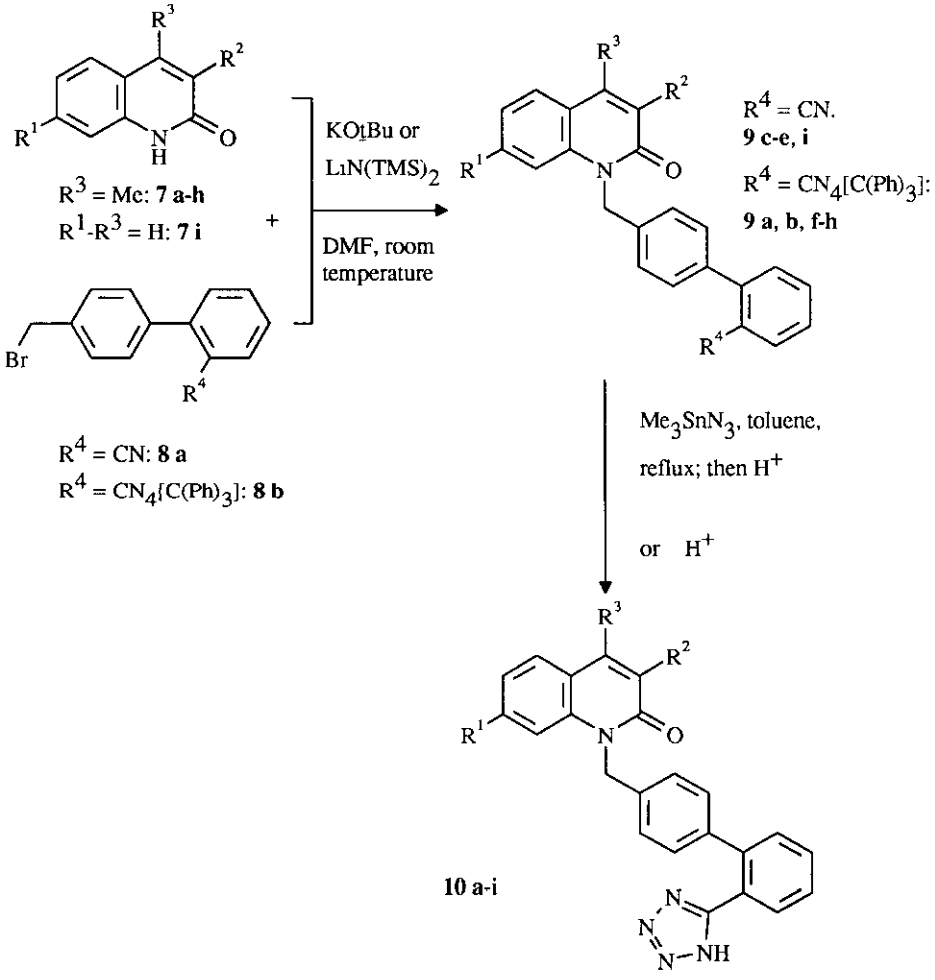


Reaction of anilines (**3a-c**) with dioxinone (**4**) led smoothly to the ß-ketoanilides (**5a-c**). Treatment of **5a-c**

with potassium *tert*-butoxide and alkyl halides afforded the corresponding 2-substituted anilides (**6a-e**) in reasonable yields. However, these compounds are accompanied by minor amounts of 2,2-disubstituted analogues, which could be easily separated and isolated in pure form by column chromatography. Acid catalyzed cyclisation of **5a-c** and **6a-e** in sulfuric acid gave 4-methylquinolin-2-ones (**7a-h**). Ring closure in **7a-g** occurred only at para position to the alkyl substituent of the phenyl moiety. In spite of the relatively mild reaction conditions the amounts of the desired products dropped to 40% in case of the substrates with acid-labile functional groups .

Scheme II describes the sequence of reactions which led to the preparation of the target molecules (**10a-i**).

Scheme II

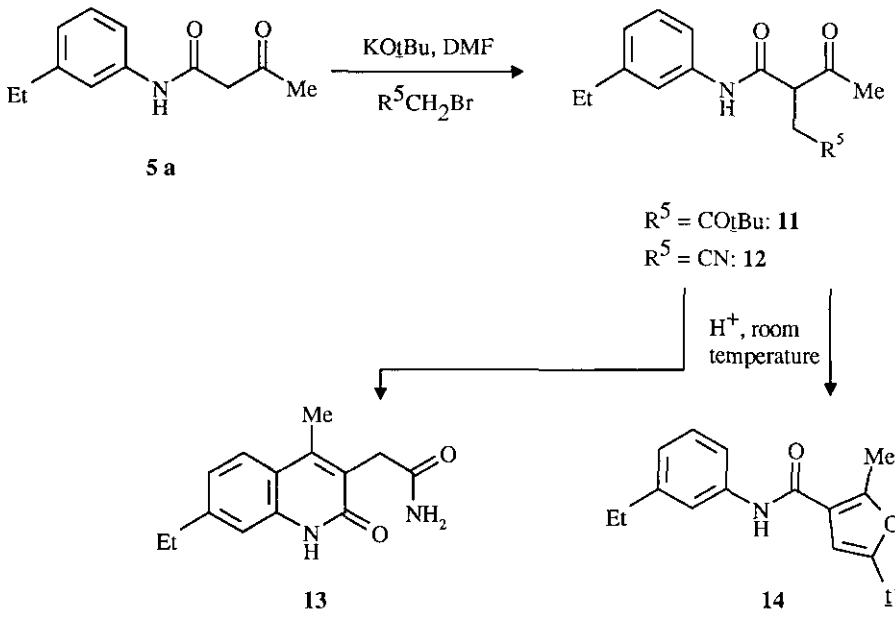


Alkylation of quinolinones (**7a-i**) with biphenylmethyl bromide (**8a**)[12] or (**8b**)[12] in the presence of potassium

tert-butoxide or lithium hexamethyldisilazide in dimethylformamide gave a mixture of two regioisomers, respectively, due to N- and O-alkylation. These isomers were separated by chromatography to give the major isomers being the desired **9a-i**. The structures of compounds (**9a-i**) were unequivocally assigned to be the 1H-substituted biphenyl derivatives by the observations of nuclear Overhauser effects on the basis of ROESY spectra.[13] The final biphenyltetrazole derivatives (**10a-i**) were readily prepared either from the corresponding nitriles (**9c-e, i**)[14] by employing trimethyltin azide[15] in refluxing toluene and subsequent acid hydolysis of the tin adduct, or removal of the trityl protecting group in **9a, b, f-h** with formic acid.

The formation of the 1H-quinolin-2-one nucleus with a keto or a cyano group in the 3-position could not be achieved under the usual cyclization conditions. According to Scheme III, ethylanilide (**5a**) was alkylated to give the *tert*-butyl ketone (**11**) or nitrile (**12**) in acceptable yields, respectively. However, treatment of **11** with sulfuric acid at room temperature afforded the condensed trisubstituted furan (**14**) exclusively. When nitrile (**12**) was exposed to these quinolin-2-one ring closure conditions, partial hydrolysis to carboxamide (**13**) occurred in good yield.

Scheme III

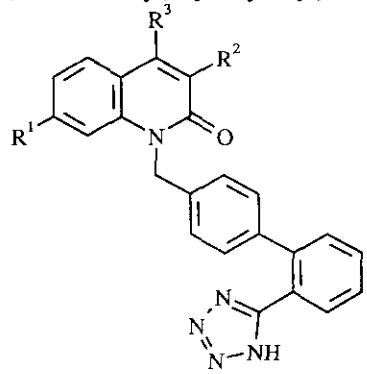


The biphenyltetrazole derivatives (**10a-i**) were evaluated for binding to angiotensin II AT_1 receptors from rat adrenal cortex (IC_{50}).[16] The selected compounds (**10d-f**) were used to see the functional antagonism of angiotensin II induced contraction of rabbit aortic rings (IC_{50})[17] and **DuP 753** was used in both assays for

comparison. Results shown in Table I indicate that receptor affinity increase with alkylsubstitution at 3 -, 4 - and 7 - positions of the quinolinone ring. However, replacement of the 3-methyl group (R^2) *in* ***10a*** *with* benzyl derivatives, **10b** and **10c** led to a significant drop in binding affinity. Introduction of carbonylmethyl functionalities at this position unexpectedly improved the biologcal activity. The most potent tetrazole analogue (**10e**) in this series displayed functional antagonism equal to **DuP 753**. We believe that this is the result of a specific receptor interaction of the amide moiety with a proton donor on one receptor side.

Table I:

Biological Activity of 1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-ones



compound	R^1	R^2	R^3	binding; IC_{50}[a](nM)	antagonism; IC_{50}[b](nM)
10i	H	H	H	23,000.0	nt
10h	H	H	CH_3	7,500.0	nt
10g	CH_3	H	CH_3	360.0	nt
10f	CH_3CH_2	H	CH_3	280.0	40.0
10a	CH_3CH_2	CH_3	CH_3	80.0	nt
10b	CH_3CH_2	CH_2Ph	CH_3	110.0	nt
10c	CH_3CH_2	$CH_2Ph(4\text{-}NO_2)$	CH_3	300.0	nt
10d	CH_3CH_2	$CH_2CO_2CH_3$	CH_3	60.0	100.0
10e	CH_3CH_2	$CH_2CON(CH_3)_2$	CH_3	10.0	3.0
DuP 753	-----	-----	-----	8.2	3.0

a = rat adrenal cortex, b = rabbit aorta, nt = not tested

In conclusion, we have described the regioselective synthesis of tetrasubstituted 1,2-dihydroquinolin-2-ones, leading to novel and potent angiotensin II antagonists.

EXPERIMENTAL

General. Melting points were determined with a Mettler FP 62 melting point apparatus and are uncorrected. Ir, nmr, and mass spectra (ms) were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250, or AM 500 (TMS as an internal standard), and a Fisons (formerly Vacuum Generator) VG 70-70E (electron-impact: ei) or 70-250SE (fast atom bombardement: fab) at 70 eV, respectively. Microanalyses were obtained with a Perkin-Elmer 240B CHN analyzer. Flash chromatography was carried out on E. Merck (Darmstadt, Germany) Kieselgel 60 silica gel (240-400 mesh). Thin-layer chromatography (tlc) was carried out on precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from E. Merck. Visualization was done with uv and I_2. Yields are not optimized. Radioligand binding studies were performed using rat adrenal cortical membranes prepared as described by Chiu *et al.*[16] Binding experiments were performed essentially as described[16] using [^{125} I] Tyr^4 angiotensin II as the radioligand. Contractile responses in rabbit aorta were determined as described elsewhere.[17]

General procedure for preparation of 3-oxobutyramides. N-(3-Ethylphenyl)-3-oxobutyramide (5a). Freshly distilled 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**4**) (18.0 g, 130 mmol) was added to a mixture of 3-ethylaniline (15.0 g, 130 mmol) in dry xylene (75 ml, isomeric mixture) at 120 °C. The resulting mixture was stirred at 120 °C for 0.5 h. During reaction evolution of acetone became apparent. The mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (9:1), to give **5a** as an oil, 25.0 g (96%); nmr (δ, ppm, DMSO-d_6): 1.16 (3H, t, J = 7.6 Hz), 1.91 (3H, s), 2.21 (3H, s), 2.57 (2H, q, J = 7.6 Hz), 3.53 (2H, s), 6.90 (1H, td, J = 1.2 and 6.3 Hz), 7.20 (1H, t, J = 6.4 Hz), 7.35-7.45 (2H, m), 9.98 (1H, br s); ms (ei), m/z = 205 (M^+). Anal. Calcd for $C_{12}H_{15}NO_2 \cdot 0.1\ H_2O$: C, 69.65; H, 7.40; N, 6.76. Found: C, 69.80; H, 7.50; N, 6.70.

N-(3-Methylphenyl)-3-oxobutyramide (5b). This compound was first described by Ewins *et al.*[18]

N-Phenyl-3-oxobutyramide (5c). This compound was first described by Knorr.[19]

General procedure for alkylation of 3-oxobutyramides. N-(3-Ethylphenyl)-2-methyl-3-oxobutyramide (6a). To a mixture of **5a** (3.0 g, 14.6 mmol) and potassium *tert*-butoxide (1.6 g, 14.6 mmol) in dimethylformamide (100 ml) at ambient temperature under nitrogen was added methyl iodide (0.9 ml, 14.6

mmol). The resulting mixture was stirred for 5 h, then poured into brine and extracted with ethyl acetate. The extract was dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (3:7), to give **6a** as white solids, 1.80 g (56%), mp 56-57 °C; nmr (δ, ppm, DMSO-d_6): 1.17 (3H, t, J = 7.6 Hz), 1.23 (3H, d, J = 7.1 Hz), 2.17 (3H, s), 2.58 (2H, q, J = 7.6 Hz), 3.65 (1H, dd, J = 7.0 and 7.0 Hz), 6.92 (1H, td, J = 1.3 and 7.6 Hz), 7.21 (1H, t, J = 7.8 Hz), 7.37-7.47 (2H, m), 10.12 (1H, br s); ms (ei), m/z = 219 (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.20; H, 7.90; N, 6.40.

2-Benzyl-N-(3-ethylphenyl)-3-oxobutyramide (6b). This compound was obtained as white solids (48%), mp 71-72 °C; nmr (δ, ppm, DMSO-d_6): 1.15 (3H, t, J = 7.6 Hz), 2.19 (3H, s), 2.55 (2H, q, J = 7.6 Hz), 3.08 (2H, d, J = 7.4 Hz), 3.95 (1H, t, J = 7.4 Hz), 6.90 (1H, td, J = 1.4 and 7.5 Hz), 7.11-7.33 (7H, m), 7.36 (1H, d, J = 1.3 Hz), 10.10 (1H, br s); ms (ei), m/z = 295 (M^+). Anal. Calcd for $C_{19}H_{21}NO_2 \cdot 0.1\ H_2O$: C, 76.82; H, 7.19; N, 4.71. Found: C, 76.90; H, 7.10; N, 4.90.

N-(3-Ethylphenyl)-2-(4-nitrobenzyl)-3-oxobutyramide (6c). This compound was obtained as white solids (75%), mp 161-162 °C; nmr (δ, ppm, DMSO-d_6): 1.15 (3H, t, J = 7.6 Hz), 2.22 (3H, s), 2.55 (2H, q, J = 7.6 Hz), 3.21 (2H, d, J = 7.4 Hz), 4.04 (1H, t, J = 7.4 Hz), 6.91 (1H, d, J = 7.6 Hz), 7.19 (1H, d, J = 7.6 Hz), 7.29-7.35 (2H, m), 7.51 (2H, d, J = 8.8 Hz), 8.13 (2H, d, J = 8.8 Hz), 10.18 (1H, br s); ms (fab), m/z = 341 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O_4 \cdot 0.25\ H_2O$: C, 66.21; H, 5.99; N, 8.13. Found: C, 66.20; H, 6.00; N, 8.10.

Methyl 3-[N-(3-ethylphenyl)carbamoyl]-4-oxopentanoate (6d). This compound was obtained as an oil (47%); nmr (δ, ppm, DMSO-d_6): 1.17 (3H, t, J = 7.6 Hz), 2.23 (3H, s), 2.58 (2H, q, J = 7.6 Hz), 2.78 (2H, dd, J = 7.1 and -17.1 Hz), 2.88 (2H, dd, J = 7.2 and -17.1 Hz), 3.60 (3H, s), 4.09 (1H, t, J = 7.2 Hz), 6.92 (1H, td, J = 1.3 and 7.6 Hz), 7.22 (1H, t, J = 7.6 Hz), 7.36-7.48 (2H, m), 10.20 (1H, br s); ms (ei), m/z = 277 (M^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.20; H, 7.00; N, 5.20.

2-Acetyl-N-(3-ethylphenyl)-N',N'-dimethylsuccinamide (6e). This compound was obtained as an oil (49%); nmr (δ, ppm, DMSO-d_6): 1.16 (3H, t, J = 7.6 Hz), 2.21 (3H, s), 2.57 (2H, q, J = 7.6 Hz), 2.76 (2H, dd, J = 6.6 and -17.4 Hz), 2.88 (2H, dd, J = 6.7 and -17.4 Hz), 2.80 (3H, s), 2.99 (3H, s), 4.09 (1H, t, J = 6.7 Hz), 6.90 (1H, d, J = 7.7 Hz), 7.20 (1H, d, J = 7.8 Hz), 7.35-7.48 (2H, m), 10.24 (1H, br s); ms (ei), m/z = 290 (M^+). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.30; H, 7.80; N, 9.60.

General procedure for preparation of 1,2-dihydroquinolin-2-ones. 7-Ethyl-3,4-dimethyl-1,2-dihy-

droquinolin-2-one (7a). A solution of **6a** (1.0 g, 4.6 mmol) in concentrated sulfuric acid (5.0 ml) was stirred at ambient temperature for 1 h. The reaction mixture was poured into ice water, and the resultant precipitates were filtered, washed with water, dried and recrystallized from ethyl acetate - hexane (1:1) to give **7a** as white solids, 0.85 g (94%), mp 207-208 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.6 Hz), 2.10 (3H, s), 2.38 (3H, s), 2.65 (2H, q, J = 7.6 Hz), 7.03 (1H, dd, J = 1.8 and 8.3 Hz), 7.10 (1H, d, J = 1.8 Hz), 7.63 (1H, d, J = 8.3 Hz), 11.52 (1H, br s); ms (ei), m/z = 201 (M^+). Anal. Calcd for $C_{13}H_{15}NO \cdot 0.1\ H_2O$: C, 76.94; H, 7.54; N, 6.90. Found: C, 76.80; H, 7.60; N, 7.20.

3-Benzyl-7-ethyl-4-methyl-1,2-dihydroquinolin-2-one (7b). This compound was prepared in 20% H_2SO_4 (20 ml) as described above and obtained as white solids (54%), mp 259-260 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.6 Hz), 2.39 (3H, s), 2.66 (2H, q, J = 7.6 Hz), 4.02 (2H, s), 7.05 (1H, dd, J = 1.8 and 8.4 Hz), 7.09-7.33 (6H, m), 7.64 (1H, d, J = 8.3 Hz), 11.68 (1H, br s); ms (ei), m/z = 277 (M^+). Anal. Calcd for $C_{19}H_{19}NO \cdot 0.2\ H_2O$: C, 80.28; H, 6.95; N, 4.99. Found: C, 80.40; H, 6.90; N, 4.80.

7-Ethyl-4-methyl-3-(4-nitrobenzyl)-1,2-dihydroquinolin-2-one (7c). This compound was obtained as white solids (58%), mp 280-281 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.6 Hz), 2.41 (3H, s), 2.66 (2H, q, J = 7.6 Hz), 4.16 (2H, s), 7.07 (1H, dd, J = 1.5 and 8.2 Hz), 7.14 (1H, s), 7.48 (2H, d, J = 8.7 Hz), 7.68 (1H, d, J = 8.2 Hz), 8.12 (2H, d, J = 8.7 Hz), 11.71 (1H, br s); ms (ei), m/z = 322 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O_3 \cdot 0.1\ H_2O$: C, 70.42; H, 5.66; N, 8.64. Found: C, 70.40; H, 5.72; N, 8.70.

Methyl 2-(7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acetate (7d). This compound was obtained as white solids (40%), mp 209-210 °C; nmr (δ, ppm, DMSO-d_6): 1.21 (3H, t, J = 7.5 Hz), 2.37 (3H, s), 2.67 (2H, q, J = 7.5 Hz), 3.60 (3H, s), 3.71 (2H, s), 7.07 (1H, dd, J = 1.8 and 8.3 Hz), 7.13 (1H, d, J = 1.6 Hz), 7.70 (1H, d, J = 8.3 Hz), 11.53 (1H, br s); ms (ei), m/z = 259 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.60; H, 6.87; N, 5.30.

2-(7-Ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-N,N-dimethylacetamide (7e). This compound was obtained as white solids (44%), mp 232-233 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.5 Hz), 2.30 (3H, s), 2.67 (2H, q, J = 7.5 Hz), 2.83 (3H, s), 3.11 (3H, s), 3.70 (2H, s), 7.05 (1H, dd, J = 1.8 and 8.3 Hz), 7.11 (1H, d, J = 1.7 Hz), 7.65 (1H, d, J = 8.3 Hz), 11.51 (1H, br s); ms (ei), m/z = 272 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_2 \cdot 0.2\ H_2O$: C, 69.69; H, 7.45; N, 10.16. Found: C, 69.80; H, 7.40; N, 10.20.

7-Ethyl-4-methyl-1,2-dihydroquinolin-2-one (7f). This compound was obtained as white solids (92%), mp 179-180 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.5 Hz), 2.40 (3H, d, J = 1.2 Hz), 2.67 (2H, q, J = 7.5

Hz), 6.31 (1H, d, J = 1.3 Hz), 7.05 (1H, dd, J = 1.8 and 8.2 Hz), 7.12 (1H, d, J = 1.7 Hz), 7.61 (1H, d, J = 8.2 Hz), 11.48 (1H, br s); ms (ei), m/z = 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO \cdot 0.4\ H_2O$: C, 74.28; H, 7.15; N, 7.22. Found: C, 74.40; H, 7.17; N, 7.10.

4,7-Dimethyl-1,2-dihydroquinolin-2-one (7g). This compound was first described by Tikotikar *et al.*[20]

4-Methyl-1,2-dihydroquinolin-2-one (7h). This compound was first described by Ochiai *et al.*[21]

General procedure for alkylation of 1,2-dihydroquinolin-2-ones. 7-Ethyl-4-methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9f). A mixture of **7f** (2.0 g, 10.7 mmol), biphenylmethyl bromide (**8b**) (7.2 g, 12.8 mmol) and potassium *tert*-butoxide (1.4 g, 12.8 mmol) in dimethylformamide (150 ml) was stirred at ambient temperature for 2 h, the reaction mixture was poured into water. The resultant precipitates were filtered, washed with water and dried. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (1:1), to give **9f** as white solids, 4.3 g (61%), mp 164-165 °C; nmr (δ, ppm, DMSO-d_6): 1.03 (3H, t, J = 7.5 Hz), 2.47 (3H, d, J = 1.2 Hz), 2.50 (2H, q, J = 7.6 Hz), 5.50 (2H, br s), 6.59 (1H, d, J = 1.3 Hz), 6.84-7.19 (12H, m), 7.26-7.76 (14H, m); ms (fab), m/z = 664 (M^+). Anal. Calcd for $C_{45}H_{37}N_5O \cdot 0.3\ H_2O$: C, 80.78; H, 5.67; N, 10.47. Found: C, 80.80; H, 5.83; N, 10.60.

7-Ethyl-3,4-dimethyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9a). This compound was obtained as white solids (64%), mp 108-109 °C; nmr (δ, ppm, DMSO-d_6): 1.06 (3H, t, J = 7.6 Hz), 2.25 (3H, s), 2.47 (3H, s), 2.50 (2H, q, J = 7.6 Hz), 5.54 (2H, br s), 6.87-6.90 (6H, m), 7.02 (2H, d, J = 8.2 Hz), 7.08 (1H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.2 Hz), 7.15 (1H, s), 7.30-7.38 (9H, m), 7.41 (1H, d, J = 7.5 Hz), 7.52 (1H, td, J = 0.9 and 7.5 Hz), 7.59 (1H, td, J = 1.2 and 7.7 Hz), 7.74 (1H, dd, J = 8.2 and 0.9 Hz), 7.77 (1H, d, J = 8.0 Hz); ms (ei), m/z = 678 (M^+). Anal. Calcd for $C_{46}H_{39}N_5O$: C, 81.51; H, 5.80; N, 10.33. Found: C, 81.40; H, 6.00; N, 10.10.

3-Benzyl-7-ethyl-4-methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one.(9b). This compound was obtained with 1.0 *M* $LiN(TMS)_2$ in THF instead of KO*t*Bu as white solids (53%), mp 154-155 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.5 Hz), 2.48 (3H, s), 2.51 (2H, q, J = 7.5 Hz), 4.17 (2H, s), 5.56 (2H, br s), 6.86-6.89 (6H, m), 7.02 (2H, d, J = 8.2 Hz), 7.07-7.18 (5H, M), 7.24-7.26 (4H, m), 7.28-7.35 (9H, m), 7.41 (1H, dd, J = 0.8 and 7.5 Hz), 7.52 (1H, td, J = 1.3 and 7.8 Hz), 7.60 (1H, td, J = 1.2 and 7.4 Hz), 7.74 (1H, dd, J = 1.2 and 7.8 Hz), 7.78 (1H, d, J = 8.3 Hz); ms (fab), m/z = 754 (M^+). Anal. Calcd for $C_{52}H_{43}N_5O \cdot 0.5H_2O$: C, 82.18; H, 5.82; N, 9.18. Found: C,

82.20; H, 6.10; N, 8.90.

4,7-Dimethyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9g). This compound was obtained as white solids (57%), mp 204-205 °C; nmr (δ, ppm, DMSO-d_6): 2.19 (3H, s), 2.49 (3H, s), 5.46 (2H, br s), 6.57 (1H, s), 6.85-6.88 (6H, m), 7.01-7.10 (5H, m), 7.15 (1H, s), 7.29-7.37 (9H, m), 7.42 (1H, dd, J = 0.8 and 7.9 Hz),7.52 (1H, td, J = 1.1 and 7.5 Hz), 7.59 (1H, td, J = 1.3 and 7.5 Hz), 7.69 (1H, d, J = 8.2 Hz), 7.74 (1H, dd, J = 1.2 and 7.8 Hz); ms (fab), m/z = 650 (M^+). Anal. Calcd for $C_{44}H_{35}N_5O$: C, 81.33; H, 5.43; N, 10.78. Found: C, 81.20; H, 4.90; N, 10.40.

4-Methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9h). This compound was obtained as white solids (61%), mp 191-192 °C; nmr (δ, ppm, DMSO-d_6): 2.49 (3H, s), 5.46 (2H, br s), 6.67 (1H, s), 6.84-6.86 (5H, m), 7.01 (2H, d, J = 8.3 Hz), 7.07 (2H, d, J = 8.3 Hz), 7.19-7.37 (12H, m), 7.41 (1H, d, J = 7.8 Hz), 7.52 (1H, td, J = 1.0 and 7.5 Hz), 7.59 (1H, td, J = 1.2 and 7.4 Hz), 7.76 (1H, dd, J = 1.0 and 7.4 Hz), 7.81 (1H, dd, J = 1.1 and 7.9 Hz); ms (ei), m/z = 636 (M^+). Anal. Calcd for $C_{43}H_{33}N_5O$: C, 81.24; H, 5.23; N, 11.02. Found: C, 81.50; H, 5.30; N, 11.30.

The following compounds were prepared with biphenylmethyl bromide (**8a**) in an analogous manner.

2-[4-((7-Ethyl-4-methyl-3-(4-nitrobenzyl)-2-oxo-1,2-dihydroquinolin-1-yl)methyl)phenyl]benzonitrile (9c). This compound was obtained as white solids (44%), mp 170-171 °C; nmr (δ, ppm, DMSO-d_6): 1.14 (3H, t, J = 7.5 Hz), 2.51 (3H, s), 2.66 (2H, q, J = 7.5 Hz), 4.31 (3H, s), 5.70 (3H, br s), 7.15 (1H, dd, J = 1.4 and 8.3 Hz), 7.33-7.38 (2H, m), 7.41 (1H, s), 7.51-7.61 (6H, m), 7.74 (1H, dd, J = 1.5 and 7.6 Hz), 7.83 (1H, d, J = 8.2 Hz), 7.91 (1H, d, J = 7.9 Hz), 8.15 (2H, d, J = 8.8 Hz); ms (fab), m/z = 514 (M^+). Anal. Calcd for $C_{33}H_{27}N_3O_3$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.00; H, 5.44; N, 7.90.

Methyl 2-[1-((2'-cyanobiphenyl-4-yl)methyl)-7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl]acetate (9d). This compound was obtained as white solids (48%), mp 115-116 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.6 Hz), 2.46 (3H, s), 2.65 (2H, q, J = 7.6 Hz), 3.63 (3H, s), 3.86 (2H, s), 5.65 (2H, br s), 7.14 (1H, dd, J = 0.9 and 8.4 Hz), 7.32 (1H, s), 7.37 (2H, d, J = 8.2 Hz), 7.47-7.62 (4H, m), 7.75 (1H, td, J = 0.9 and 7.2 Hz), 7.81 (1H, d, J = 8.2 Hz), 7.91 (1H, dd, J = 0.9 and 7.8 Hz); ms (fab), m/z = 451 (M^+). Anal. Calcd for $C_{29}H_{26}N_2O_3 \cdot 0.2\ H_2O$: C, 76.72; H, 5.86; N, 6.17. Found: C, 76.70; H, 5.90; N, 6.10.

2-[1-((2'-Cyanobiphenyl-4-yl)methyl)-7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl]-N,N-dimethylacetamide (9e). This compound was obtained as white solids (46%), mp 189-190 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.6 Hz), 2.39 (3H, s), 2.62 (2H, q, J = 7.6 Hz), 2.85 (3H, s), 3.15 (3H, s), 3.83 (2H, s),

5.63 (2H, br s), 7.14 (1H, dd, J = 1.0 and 8.4 Hz), 7.30 (1H, s), 7.36 (2H, d, J = 8.3 Hz), 7.51-7.59 (4H, m), 7.76 (1H, td, J = 1.1 and 7.8 Hz), 7.79 (1H, d, J = 8.3 Hz), 7.91 (1H, dd, J = 0.8 and 7.8 Hz); ms (ei), m/z = 464 (M^+). Anal. Calcd for $C_{30}H_{29}N_3O_2$: C, 77.73; H, 6.31; N, 9.06. Found: C, 77.70; H, 6.40; N, 9.20.

2-[4-((2-Oxo-1,2-dihydroquinolin-1-yl)methyl)phenyl]benzonitrile (9i). This compound was obtained from 2-hydroxyquinoline (**7i**) as white solids (52%), mp 175-176 °C; nmr (δ, ppm, DMSO-d_6): 5.61 (2H, br s), 6.81 (1H, d, J = 9.4 Hz), 7.16-7.78 (13H, m); ms (ei), m/z = 336 (M^+). Anal. Calcd for $C_{23}H_{16}N_2O \cdot 0.5\ H_2O$: C, 80.04; H, 4.96; N, 8.12. Found: C, 79.90; H, 5.10; N, 8.00.

General procedure for preparation of tetrazoles. Methyl 2-[7-ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]acetate (10d). Compound (**9d**) (0.8 g, 1.7 mmol) was allowed to reflux with trimethyltin azide (1.7 g, 8.5 mmol) in toluene (25 ml). The reaction mixture was stirred for 30 h and concentrated in vacuo to an oil. The residue was taken up in ice-cold, dry methanol (50 ml) saturated with HCl gas. The resulting mixture was stirred for 10 min before it was concentrated in vacuo. Flash chromatography (10% methanol in ethyl acetate as eluent) and recrystallisation from ethanol provided **10d** as white solids, 0.53 g (65%), mp 215-216 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.5 Hz), 2.44 (3H, s), 2.65 (2H, q, J = 7.5 Hz), 3.62 (3H, s), 3.82 (2H, s), 5.54 (2H, br s), 7.00-7.25 (6H, m), 7.46-7.68 (4H, m), 7.80 (1H, d, J = 8.3 Hz); ms (fab), m/z = 494 (M^+). Anal. Calcd for $C_{29}H_{27}N_5O_3 \cdot 0.6\ H_2O$: C, 69.08; H, 5.63; N, 13.89. Found: C, 69.10; H, 5.53; N, 13.80.

7-Ethyl-4-methyl-3-(4-nitrobenzyl)-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10c) This compound was obtained as white solids (81%), mp 228-229 °C; nmr (δ, ppm, DMSO-d_6): 1.12 (3H, t, J = 7.5 Hz), 2.48 (3H, s), 2.64 (2H, q, J = 7.5 Hz), 4.28 (2H, s), 5.57 (2H, br s), 7.04 (2H, d, J = 8.3 Hz), 7.13 (1H, dd, J = 0.9 and 8.3 Hz), 7.16 (2H, d, J = 8.3 Hz), 7.24 (1H, s), 7.48-7.57 (4H, m), 7.62-7.67 (2H, m), 7.79 (1H, d, J = 8.3 Hz), 8.14 (2H, d, J = 8.8 Hz); ms (fab), m/z = 557 (M^+). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.10. Found: C, 71.30; H, 5.15; N, 15.10.

2-[7-Ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]-N,N-dimethylacetamide (10e). This compound was obtained as white solids (55%), mp 225-226 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.6 Hz), 2.38 (3H, s), 2.65 (2H, q, J = 7.6 Hz), 2.85 (3H, s), 3.15 (3H, s), 3.82 (3H, s), 5.53 (2H, br s), 7.03 (2H, d, J = 8.2 Hz), 7.13 (1H, dd, J = 0.9 and 8.4 Hz), 7.16 (2H, d, J = 8.2 Hz), 7.22 (1H, s), 7.50 (1H, d, J = 7.8 Hz), 7.55 (1H, td, J = 0.9 and 8.2 Hz), 7.61-7.66 (2H, m), 7.77 (1H, d, J = 8.3 Hz); ms (fab), m/z = 507 (M^+). Anal. Calcd for $C_{30}H_{30}N_6O_2 \cdot 0.2\ H_2O$: C, 70.64; H, 6.01; N,

16.48. Found: C, 70.60; H, 6.10; N, 16.50.

1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10i) This compound was obtained as white solids (72%), mp 265-266 °C; nmr (δ, ppm, DMSO-d_6): 5.52 (2H, br s), 6.73 (1H, d, J = 9.5 Hz), 7.04 (2H, d, J = 8.2 Hz), 7.15 (2H, d, J = 8.2 Hz), 7.25 (1H, t, J = 7.5 Hz), 7.40 (1H, d, J = 8.6 Hz), 7.50-7.58 (4H, m), 7.63-7.68 (2H, m), 7.76 (1H, dd, J = 1.5 and 7.5 Hz), 8.00 (1H, d, J = 9.5 Hz), 16.25 (1H, br s); ms (fab), m/z = 381 (M^+). Anal. Calcd for $C_{23}H_{17}N_5O \cdot 1.1\ H_2O$: C, 69.21; H, 4.85; N, 17.54. Found: C, 69.20; H, 4.70; N, 17.54.

General procedure for deprotection of tetrazoles. 7-Ethyl-4-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2 dihydroquinolin-2-one (10f). A mixture of **9f** (0.5 g, 0.75 mmol) , formic acid (5 ml) and methanol (45 ml) was stirred at 50 °C for 2 h. The solution was concentrated in vacuo and the residue was triturated with methanol to give **10f** as white solids, 278 mg (88%), mp 260-261 °C; nmr (δ, ppm, DMSO-d_6): 1.11 (3H, t, J = 7.5 Hz), 2.45 (3H, d, J = 1.1 Hz), 2.64 (2H, q, J = 7.5 Hz), 5.50 (2H, br s), 6.56 (1H, d, J = 1.2 Hz), 7.00-7.23 (6H, m), 7.46-7.73 (5H, m), 16.60 (1H, br s); ms (ei), m/z = 421 (M^+). Anal. Calcd for $C_{26}H_{23}N_5O \cdot 0.1\ H_2O$: C, 73.79; H, 5.52; N, 16.55. Found: C, 73.70; H, 5.62; N, 16.80.

7-Ethyl-3,4-dimethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10a). This compound was obtained as white solids (61%), mp 242-243 °C; nmr (δ, ppm, DMSO-d_6): 1.12 (3H, t, J = 7.6 Hz), 2.21 (3H, s), 2.43 (3H, s), 2.62 (2H, q, J = 7.6 Hz), 5.53 (2H, br s), 7.00-7.20 (6H, m), 7.46-7.70 (4H, m), 7.74 (1H, d, J = 8.2 Hz), 11.20 (1H, br s); ms (fab), m/z = 436 (M^+). Anal. Calcd for $C_{27}H_{25}N_5O$: C, 74.46; H, 5.79; N, 16.08. Found: C, 74.70; H, 5.60; N, 16.00.

3-Benzyl-7-ethyl-4-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10b). This compound was obtained as white solids (72%), mp 137-138 °C; nmr (δ, ppm, DMSO-d_6): 1.13 (3H, t, J = 7.6 Hz), 2.46 (3H, s), 2.64 (2H, q, J = 7.6 Hz), 4.15 (2H, s), 5.58 (2H, br s), 7.04 (2H, d, J = 8.3 Hz), 7.12 (1H, dd, J = 0.9 and 8.4 Hz), 7.14-7.18 (3H, m), 7.22-7.28 (5H, m), 7.50 (1H, d, J = 7.7 Hz), 7.54 (1H, td, J = 0.8 and 7.3 Hz), 7.62-7.67 (2H, m), 7.77 (1H, d, J = 8.3 Hz); ms (fab), m/z = 512 (M^+). Anal. Calcd for $C_{33}H_{29}N_5O \cdot 0.3\ H_2O$: C, 76.68; H, 5.77; N, 13.55. Found: C, 76.70; H, 5.80; N, 13.30.

4,7-Dimethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10g). This compound was obtained as white solids (73%), mp 279-280 °C; nmr (δ, ppm, DMSO-d_6): 2.35 (3H, s), 2.45 (3H, d, J = 1.2 Hz), 5.48 (2H, br s), 6.55 (1H, d, J = 1.2 Hz), 7.00-7.16 (5H, m), 7.22 (1H, s), 7.48-7.72

(5H, m), 16.20 (1H, br s); ms (fab), m/z = 408 (M^+). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19. Found: C, 73.40; H, 5.20; N, 17.20.

4-Methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10h). This compound was obtained as white solids (70%), mp 280-281 °C; nmr (δ, ppm, DMSO-d_6): 2.48 (3H, d, J = 1.3 Hz), 5.50 (2H, br s), 6.63 (1H, d, J = 1.3 Hz), 7.00-7.15 (4H, m), 7.26 (1H, td, J = 1.2 and 8.2 Hz), 7.38 (1H, dd, J = 1.2 and 8.6 Hz), 7.47-7.70 (5H, m), 7.81 (1H, dd, J = 1.6 and 8.0 Hz), 16.25 (1H, br s); ms (fab), m/z = 394 (M^+). Anal. Calcd for $C_{24}H_{19}N_5O \cdot 0.3\ H_2O$: C, 72.31; H, 4.97; N,17.57 . Found: C, 72.30; H, 4.80; N, 18.00.

2-Acetyl-N-(3-ethylphenyl)-5,5-dimethyl-4-oxocaproamide (11). This compound was obtained by the method described for **6a** as white solids (48%), mp 121-122 °C; nmr (δ, ppm, DMSO-d_6): 1.10 (9H, s), 1.17 (3H, t, J = 7.5 Hz), 2.21 (3H, s), 2.58 (2H, q, J = 7.5 Hz), 2.98 (2H, dd, J = 6.4 and -18.3 Hz), 3.17 (2H, dd, J = 6.4 and -18.3 Hz), 4.05 (1H, t, J = 6.4 Hz), 6.91 (1H, d, J = 7.5 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.36-7.46 (2H, m), 10.24 (1H, s); ms (ei), m/z = 303 (M^+). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.30; H, 8.50; N, 4.70.

2-Cyanomethyl-N-(3-ethylphenyl)-3-oxobutyramide (12). This compound was obtained as an oil (41%), nmr (δ, ppm, DMSO-d_6): 1.18 (3H, t, J = 7.6 Hz), 2.24 (3H, s), 2.59 (2H, q, J = 7.6 Hz), 2.90 (2H, d, J = 7.1 Hz), 4.07 (1H, t, J = 7.1 Hz), 6.97 (1H, d, J = 7.6 Hz), 7.25 (1H, t, J = 7.6 Hz), 7.37-7.47 (2H, m), 10.52 (1H, br s); ms (ei), m/z = 244 (M^+). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 0.05\ H_2O$: C, 68.59; H, 6.62; N, 11.43. Found: C, 68.50; H, 6.50; N, 11.40.

2-(7-Ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acetamide (13). This compound was obtained by the method described for **7a** as white solids (60%), mp 289-290 °C; nmr (δ, ppm, DMSO-d_6): 1.20 (3H, t, J = 7.5 Hz), 2.36 (3H, s), 2.66 (2H, q, J = 7.5 Hz), 3.50 (2H, s), 6.79 (1H, br s), 7.05 (1H, dd, J = 1.8 and 8.3 Hz), 7.11 (1H, d, J = 1.7 Hz), 7.20 (1H, br s), 7.66 (1H, d, J = 8.3 Hz), 11.52 (1H, br s); ms (ei), m/z = 244 (M^+). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 1.8\ H_2O$: C, 60.81; H, 7.13; N, 10.13. Found: C, 60.90; H, 7.30; N, 10.10.

The following compound was prepared in an analogous manner. **5-*tert*-Butyl-N-(3-ethylphenyl)-2-methylfuran-3-carboxamide (14).** This compound was obtained as white solids (75%), mp 134-135 °C; nmr (δ, ppm, DMSO-d_6): 1.19 (3H, t, J = 7.5 Hz), 1.26 (9H, s), 2.51 (3H, s), 2.59 (2H, q, J = 7.5 Hz), 6.68 (1H, s), 6.91 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.8 Hz), 7.53 (1H, d, J = 7.9 Hz), 7.56 (1H, s), 9.49 (1H, s); ms

(ei), m/z = 285 (M^+). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 8.30; N, 4.80.

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